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| EXAMINER | |
|---|---|
| CROUCH, D | |
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**DATE MAILED:** 03/18/99

**Please find below and/or attached an Office communication concerning this application or pr ceeding.**

**Commissioner of Patents and Trademarks**

| Office Action Summary | Application No. 08/993,564 | Applicant(s) Newman |
|---|---|---|
| | Examiner Deborah Crouch | Group Art Unit 1632 |

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three (3)* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claims**

☒ Claim(s) *1-36* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-36* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

**Application Papers**

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *4*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

*--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---*

## DETAILED ACTION

Claims 1-36 are pending in the instant Application.

### *Claim Rejections - 35 USC § 101*

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-9 and 13-36 are rejected under 35 U.S.C. 101 because the claimed invention is directed to nonstatutory subject matter.

The claimed invention is not considered to be patentable subject matter under 35 U.S.C. 101 because the broadest reasonable interpretation of the claimed invention as a whole embraces a human being. In particular, applicant's claimed invention as set forth in all the independent claims is not limited to non-humans but rather includes within its scope a human being and as such falls outside the scope of protection under 35 U.S.C. 101.

The question of patentable subject matter under 35 U.S.C. 101 is decided on a case-by-case basis (see MPEP 2105). As noted by the Supreme Court in *Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980), the relevant legislative history of 35 U.S.C. 101 showed that "Congress intended statutory subject matter to 'include anything under the sun that is made by man'." 447 U.S. at 308-309, 206 USPQ at 197. However, the Court pointed out that "[t]his is not to suggest that § 101 has no limits or it embraces every discovery. The laws of nature, physical phenomena, and abstract ideas have been held not patentable." 447 U.S. at 309, 206 USPQ at 197.

While the PTO recognizes that the scope of protection covered by 35 U.S.C. 101 is expansive and the fact that a claimed invention which embraces a human being is not within one of the exclusions enumerated by the Supreme Court in *Chakrabarty*, *i.e.*, the laws of

nature, physical phenomena and abstract ideas, the PTO believes that Congress did not intend 35 U.S.C. 101 to include the patenting of human beings.

The Supreme Court in *Chakrabarty* exercised judicial restraint and chose not to decide the issue of whether a claim embracing human beings is considered to be patentable subject matter under 35 U.S.C. 101. The claim before the Supreme Court in *Chakrabarty* was directed to a microorganism. The Supreme Court did not have to reach and did not reach a determination as to whether human being is considered to be statutory subject matter under 35 U.S.C. 101. However, the Supreme Court did recognize that not every discovery is covered by 35 U.S.C. 101. For more than 10 years the PTO has consistently taken the position that a claim directed to or including within its scope a human being is not considered to be patentable subject matter under 35 U.S.C. 101 (see 1077 OG 24, April 21, 1987). Since applicant's claimed invention embraces a human being, it is not considered to be patentable subject matter under 35 U.S.C. 101.

For the reasons noted above, the claimed invention as a whole is directed to nonstatutory subject matter, which is not protectable under 35 U.S.C. 101.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention so that it will operate as intended without undue experimentation.

**The specification fails to provide an enabling disclosure for h w t make and use the claimed invention because the teachings of the specificati n fail to provide the required teachings and exemplifications that would have permitted the artisan**

**t have prepared the chimeric embryos and animals as instantly claimed and as described in the specification without undue experimentation.**

The invention of claims 13-18 are drawn to chimeric animals, where the chimerism is human/animal. However, the specification fails to provide an enabling disclosure for the preparation of any animals that derive from human chimeric embryos because given the state of the art and the nature of the invention, one would not have been able to generate viable progeny of human chimeras without specific guidance that is lacking in the specification as originally filed. In regard to claims 1-12 and 19-36, drawn to human/non-human animal chimeric embryos and cell lines developed from such chimeric embryos, rather than to animals *per se*, it is noted that within the specification at page 1, lines 1-4, it is stated that:

> The invention relates to chimeric embryos and chimeric animals created from human embryos or embryonic stem cells and embryos or ES cells from one or more non-human animals, which have been aggregated under conditions in which a **viable embryo form** (Emphasis added).

Therefore, since as supported below, the specification fails to provide an enabling disclosure for how to prepare embryos that give rise to any human/non-human animal chimeras, and since viable chimeric embryos may be considered to be those that give rise to independent animals and/or human beings, the specification fails to provide an enabling disclosure for how to make the claimed chimeric animals, chimeric embryos and cell lines as claimed without undue experimentation.

In regard to the nature of interspecies chimeras, (as are the claimed human/non-human animal chimeric embryos, animals developed from the embryos , and cell lines developed from the chimeric embryos), the art at the time of filing indicates that among problems with unpredictable outcomes are the loss of one species contribution over another, and that such loss is without *a priori* prediction of which of the parental species are lost, and a lack of fecundity of chimeric animals that may be formed under particular circumstances.

Such unpredictability is evidenced by consideration of the sheep-goat chimeras reported by Fehilly et al. (1984) Nature 307, 634-638 (referenced in the instant specification

at page 2, first paragraph). The chimeric animals that were produced "had the general appearance of lambs, but in three of these animals the fleece had transverse bands and patches of hair contrasting sharply with the surrounding densely curled wool" (see page 635, second column, full paragraph therein). Thus the chimeras had contributions from both goat and sheep "parents". However, as noted by Fehilly, there was no prediction as to what percentage of the chimera was from the goat parent or how much was from the sheep parent. In addition, Fehilly et al. (1985) J. Reprod. Fert. 74, 215-221 disclosed that in the production of chimeric goat-sheep, there were biases towards chimeras whose genotype and phenotype was most like that of the recipient, and that the successful production of chimeras resided in the neutralization of incompatibility between the chimeric embryo (see page 221, para. 1). To achieve neutralization in the goat-sheep chimera required particular means of chimeric embryo construction that included means of controlling the formation of and contribution by the donor embryo cells of the chimera (see page 221, para. 1). However, the present specification, fails to provide any guidance as to the parameters to be used for controlling chimeric embryo chimerism and/or the structure of the chimeric embryos formed such that viable embryos which give rise to viable human/non-human animals can be made with any prediction without undue experimentation. That this issue remains in the development and establishment of chimeric embryos is supported by reference to Ruffing et al. (1993) Biol. Reprod. 48, 889-904, which states on page 889, second column, that

> The results of the descriptive analysis on chimerism in the conceptus were used to evaluate the importance of the relative ages of the blastomeres in the chimeric embryo in the distribution of chimerism in the conceptus and, in addition, to examine the effects of chimerism on pregnancy outcome, including fetal and placental growth.

In these studies, reference to Table 1, on page 893, reveals that the number of term offspring is variable dependent upon the host used to carry the chimeric embryo, and that even so, no animals that were fecund were reported. Thus, while the specification relies upon the results and techniques reported from the generation of sheep-goat chimeras (see, e.g., specification

at page 3, last paragraph), no guidance is present in applicant's specification as to how one would extend or adapt the techniques employed for the production of goat-sheep chimeras to those that would include humans and any other animals or non-human primates, to obtain a human/non-human animal chimera without undue experimentation.

All of these uncertainties and unpredictabilities are further enhanced when one considers the scope of the invention as presently claimed. In claims 1-9, and 13-15, the claimed chimeric embryos are prepared from a human and "one or more" second animals species. In claims 28-36, the claims include chimeras prepared from a human and one or more second species selected from the group "comprising" several primates, pigs, mice, rats, and rabbits (note that the language of the claim is not closed and therefore, includes any animal, although only several species are recited). Two basic points are apropos to the scope of the claims. First, the claims include chimeras prepared between two **or more** parental cells. However, any problems that would be associated with preparing chimeric embryos and animals from two species would have been expected to have been greater when more than two species were present since the number of cell interactions that would need to be considered would be geometrically multiplied. To illustrate: In a two way chimera, three sets of cellular interactions are present; human/human, human/animal, and animal/animal. In contrast, in a three way chimera, seven sets of cellular interactions are present; human/human, human/animal 1, human/animal 2, animal 1/animal 1, animal 1/animal 2, animal 2/animal 2, and human/animal 1/animal 2. Further, with the exception of the recitation of "one or more" animal donors in the claimed chimeras, the specification is silent as to how such would be made or used.

The second problem with formation of chimeras between diverse animals may be best illustrated by reference to embryonic formation between animals extending across a relatively limited phylogenetic range (sea urchin, amphibian, avian, and mammal). Reference to Figure 2-1 of Ham and Veomet, at page 16, shows the widely diverse pattern of embryonic

development among these representative animals (Mechanisms of Development, R.G. Ham and M.J. Veomett, authors, C.V. Mosby Co., St. Lous, 1980). However, the specification is silent in regard to any guidance as to how one would make and use, without undue experimentation, chimeric embryos and animals generated between such a diverse set of animals and indeed how one would have addressed the differences that exist in the fundamental manner in which the embryos develop. In the absence of such guidance, the artisan would not have been able to have prepared and used chimeras between such phylogenetically diverse animals without undue experimentation.

Furthermore, the specification discloses numerous uses for the claimed embryos and animals. Such uses including studying regulation of differentiation, teratology, toxicology, and in the creations of model systems for clinical testing (see specification at pages 7 and 8). However, as the making of human/non-human animals is seen as not enabled, the specification also fails to teach how to make human/non-human chimeras, without undue experimentation, for the disclosed uses.

**The specification further fails to provide an enabling disclosure for the preparation of chimeric human embryos and animals that require the use of embryonic stem (ES) cells from said humans and/or cognate animals because the specification fails to provide an enabling disclosure in regard to how one would have prepared such cells and the art at the time of filing of the present specification indicates that the preparation of such cells would not have been considered to have been within the level of skill of the artisan.**

In order to prepare the claimed chimeric embryos and animals of claims 2-7, 10-18, 20-25 and 29-34 using ES cells, the artisan required guidance regarding the preparation of preblastocyst embryos, the placement of such cells in *in vitro* culture and the fusion of any resultant cell lines with host embryos. At the time of filing, the art regarded as unpredictable the obtaining of ES cells that would contribute to the germ line of the resultant animal. In particular, the unpredictability and variability of establishment of embryonic stem cells is evidenced by data taken from a single species, mouse, as reviewed by Baribault et al. (1989) Mol. Biol. Med. 6, 481-492. In Table 1 of Baribault et al., data is presented in regard to the

ability of embryonic stem (ES) cells derived from various strains of mice to contribute to germ line chimerism, that is contributions by both parental embryonic cell types. It is noted that dependent upon the strain of mice from which the ES cells were derived, the frequency of germ line chimerism (a hallmark of an ES cell line) ranged from 1% to 19%. Thus, even within a single species, the establishment of ES cells was highly variable and unpredictable. Such variability would have been expected to have been even greater when one considered crossing species boundaries, and the practitioner would not have accepted assertions of establishment of ES cells from species other than mice in the absence of supporting data evidencing not only the establishment of cells in culture but also demonstrating the ability of such cells to contribute to the germ line of host animals. This requirement of the artisan is evidenced by Bradley et al., which states within the paragraph bridging pages 537 and 538 that

> A number of reports have claimed the isolation of ES cells from farm animals such as pigs and sheep. However, the description of these cell lines is yet to be supported by documentation that they can proliferate and differentiate in an embryo *in vivo*, contributing to somatic tissues or germ cells (Bradley et al. (1992) Bio/Technology 10, 534-539).

Thus, the artisan required such evidence in order to accept the validity of the establishment of ES cells and the instant application lacks such evidence. Further evidence for the lack of correlation between conditions of manipulating at least ES cells to be prepared from different species comes from the reference to Saito et al., which states in the second paragraph of the discussion that

> It is essential for ES cell culture to investigate the optimal medium conditions of early preimplantation embryos. In the bovine, continuous culture of cells from a day-11-embryo was achieved on polystyrene in fetal bovine serum...In sheep, Handyside et al. used a mouse STO fibroblast or sheep fibroblast line as the feeder-layer for culture of the ICM [inner cell mass]. They did not observe colonies with an ES-like morphology. Piedrahita et al. did not obtain ovine cell lines with an ES-like morphology when plated on mouse STO feeder-layers or STO with BRL-conditioned medium. These findings suggest species differences in terms of the conditions required for ES-cell cultures. In addition, LIF-conditioned medium has been shown to enable the formation of murine ES cells in the absence of feeder cells. It is currently not fully understood which role feeder cells and their differentiation inhibitory activity

> contained in LIF- or BRL-conditioned media play in promoting the continuing proliferation and in inhibiting the differentiation of ES cells (Saito et al. (1992) Roux's Arch. Dev. Biol. 201, 134-141).

The criticality of the teachings required for the preparation of ES cells is further evidenced by the reference to Gardner et al.. In reviewing the extant state of the ES cell art up to that time, the reference to Gardner et al. states in its abstract that:

> Remarkably little is known about mammalia embryonic stem (ES) cells despite their very widespread use in studies on gene disruption and transgenesis. As yet, it is only in the mouse that lines of ES cells which retain the ability to form gametes following reintroduction into the early conceptus have been obtained. Even in this species, most strains have so far proved refractory to the derivation of such cell lines. Apart from persisting ignorance as to how the various procedures that have been claimed to improve success actually do so, even the tissue of origin of ES remains uncertain (Gardner et al. (1997) Int. J. Devel. Biol. 41, 235-243).

Thus, these teachings indicate not only that ES cells have not been prepared across species despite significant effort by the artisan, but also indicate that the animals from which ES cells are to be prepared must be considered and represent a factor contributing to the unpredictability of the establishment and use of ES cells. In particular, even in the well-studied mouse system where many inbred strains were available, not all strains were equal when preparing ES cells. This problem is exacerbated when one considers that the instantly claimed invention is drawn to humans and other animal species in which well characterized, genetically uniform, strains are not available and unlikely to be generated given that many animals in general, and primates in particular, have long generation times, and limited abilities to be inbred in the absence of the large numbers of animals that are required to be culled to generate viable strains.

Therefore, given the unpredictable nature of the claimed invention, the artisan would have been required to have exercised undue experimentation in the elaboration of which particular combinations of donor species that would result a human/non-human animal chimera for each particular combination. In addition, given the lack of guidance and unpredictability in obtaining ES cells for the breadth of the claims as supported by the teachings of the art at the time of filing that the establishment and culture of ES cells was unpredictable, the production of chimeric human/non-human animal chimera from ES cells is also not enabled. In the absence of additional guidance from the specification as to the methodology for the formation of human/non-human animal chimeras that would give rise to a viable chimeric animal of any particular degree of chimerism, the skilled artisan would not

have been able to practice the claimed invention at the time of filing in the absence of significant, unpredictable experimentation, which is considered to be undue. Consequently, as the specification fails to provide any particular guidance whatsoever in regard to how one would have prepared any human chimeric animals or embryos, the specification fails to provide an enabling disclosure for any embodiment of what is claimed.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-36 are vague and indefinite in regard to the requirements for what would be considered to be a chimeric embryo within the scope of claims. At page 1, lines 4 and 5, it is indicated that chimeric embryos and animals are required to be "viable embryo forms." However, it is unclear as to what would be considered to be such a form. Further, at pages 19-21, it is acknowledged that not all chimeras within the scope of the claims would be viable (i.e., give rise to any animal). Thus, applicant has not pointed out and distinctly claimed their invention such that the meets and bounds of the subject matter is clear.

Claims 1,5-7, 9, 19,23-25, 27, 28,32-34 and 36 are vague and indefinite because claims 1, 19, and 28 recite one or more second animal species and claims under consideration recite characteristics of the cell from the second animal species. However, since multiple second animal species are recited, it is unclear as to which of these species are referred.

Similarly, claims 1, 9, 10, 12, 13, 15, 19, 27, 28 and 36 are vague and indefinite because it is unclear as to which of said one or more second animal species have the transgene and if the one or more transgenes are required to be in one or several of the cells of the species of second animal cell.

Claims 10, 13, and 28 are vague and indefinite because it is unclear as to the scope of what is being claimed. The claims use a hybrid linking phrase "selected from the group **comprising**...". The phrase used when reciting a Markush group of elements, which is a closed set of alternatives, is "selected from the group **c nsisting of**...". Therefore, it is

unclear as to what is being claimed, or if applicant mistakenly used "comprising" instead of "consisting of" (see MPEP 2173.05(h)(a)). Clarification is requested.

Claims 13-15 are vague and indefinite because the use of the phrase "developed from a chimeric embryo" makes it unclear as to whether the claims are drawn to chimeric animals or to the progeny of chimeric animals.

Similarly, claims 10-12 are vague and indefinite because it is unclear as to what would be required for a cell to be "developed" from a chimeric embryo and how such would be distinguishable from a cell prepared from any other source.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7, and 13-25 are rejected under 35 U.S.C. 102(b) as being anticipated by Zanjani et al. (1996) Int. J. Hematol. 63, 179-192 or Almeida-Porada et al. (1996) Experimental Hematol. 24, 482-487.

Each of Zanjani et al. and Almeida-Porada et al. discloses the introduction of human hematopoietic cells into sheep *in utero*. Therefore, in so far as the claimed embryo chimeras read on the combination of sheep and human cells, each of these references anticipates what is claimed.

Claims 1-7, and 13-25 and 28-34 are rejected under 35 U.S.C. 102(b) as being anticipated by Pixley et al (1994) Pathobiol. 62, 238-244.

Pixley et al. disclose the introduction of human hematopoietic cells into mice *in utero*. Therefore, in so far as the claimed embryo chimeras read on the combination of mice and human cells, each of these references anticipates what is claimed.

Claims 10-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Cheng et al. (1994) Develop. 120, 3145-3153.

The claimed invention is drawn to cells prepared from chimeric embryos wherein the chimeric donors are a human and a non-human. Therefore, in so far as the claimed cells, once isolated, read on any non-human cells, the claimed cell lines read on the mouse primordial germ cells disclosed by Cheng et al., (see e.g. Abstract). Thus, Cheng anticipates what is claimed.

Note that in regard to the limitation that the one or more of the donor cells harbor transgenes, the animals that are prepared from the chimeras may not harbor any transgene if the germ cell from which the animals derive did not harbor a transgene.

Claims 10-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Catalog of Cell Lines and Hybridomas, 7th ed., American Type Culture Collection (ATCC), Rockville, MD. 20852-1776, 1992, entry HTB 157, HTB 158, and HTB 160, page 271.

In so far as the claimed cell lines read on those that are prepared from human embryos or fetuses, the indicated ATCC HTB human fetal and embryo cell lines (Fhs 738Lu, Fhs 173We, and Fhs 738BI) anticipate what is claimed.

Note that in regard to the limitation that the one or more of the donor cells harbor transgenes, the animals that are prepared from the chimeras may not harbor any transgene if the germ cell from which the animals derive did not harbor a transgene.

Claims 13-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Bradley et al. (1992) Bio/Technology 10, 534-539.

As noted above, in regard to claims 13-15, it is unclear as to whether the claimed animals are drawn to human/animal chimeras or to animals that are the progeny of such animals. In so far as these claims read on the progeny of chimeric animals and therefore overlap with the descendants defined in claims 16-18, the claims read on the "one or more second animal species" that is recited in claim 13. While the claims recite process language regarding how the claimed animals and descendants were prepared, the products that would result from, for example, a chimera formed between a human and a mouse, could be indistinguishable from a mouse prepared by any other means. Therefore, in so far as the claims read on the second animal, the claimed invention is anticipated by Bradley et al. which discloses transgenic mice (see e.g. Figure 1).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-7, 19-25 and 28-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gustafson et al. (1993) J. Reprod. Fert. 99, 267-273.

Gustafson et al. teaches that five sheep-goat chimeras received hybrid embryos and developed pregnancies as determined by ultrasonography (page 269, col. 1, para. 2, lines 1-4). The hybrid embryos were the result of breeding between a goat doe and an ovine ram (page 268, col. 1, para. 1, lines 1-3). Of the five, one chimera, 8810, returned to estrus on day 46, indicating a failure to maintain pregnancy (page 269, col. 1, para. 2, lines 4-6). On day 31, 8809 and 8811 showed irregularities in the uterine wall and by day 40, placentome formation in all four chimeras was evident (page 269, col. 1, para. 2, lines 6-9). Heartbeats were detected in the four fetuses on day 35, and were used to establish fetal viability (page 269, col. 1, para. 2, lines 11-13). In 8702 and 8806, fetal movement was also detected (page 269, col. 1, para. 2, lines 13-16). Chimera 8811, was the first to resorb the hybrid pregnancy, followed by 8809, 8806 and 8702 (page 269, col. 1, para. 3, line 1 to page 270, col. 1, para. 1, line 3). Gustafson et al. provides motivation in stating that the establishment of chimeric goat-sheep pregnancies with chimeric goat-sheep embryos is to analyze the influence on the maternal environment on placental function in the chimeric foster mother (page 273, col. 1, para. 1, lines 7-10). Thus at the time of the instant invention, it would have been obvious to the ordinary artisan to make chimeric human animal embryos given the teachings and motivation of Gustafson et al. Such an analysis would be of obvious benefit in determining factors that lead to placental failure. A reasonable expectation of success is provided as the claims state only chimeric embryos, without stating any size or age limitation, or developmental potential. Thus for achieving an embryo, which can be as small as one cell, Gustafson et al. provides sufficient teachings and motivation

Claims 1, 8, 9, 19, 25-28 and 35 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Watanabe et al. (1992) Develop. 114, 331-338 in view of Robertson et al. (1986) Nature 323, page 445-448.

Watanabe et al. teach the production of chick-quail chimeric embryos by injecting quail stage XI-XIII blastoderm cells into stage XI-XIII and stage XIV-2 chick blastoderms *in ovo* (page 332, col. 1, para. 1, lines 3-6 and 16-24). The descendants of the donor quail cells were then determined by histological analysis of the chimeric embryos after 9 days of incubation (page 332, col. 1, para. 2, lines 1-4). The analysis shows that the location of injection of the quail cells determined the site of chimerism (page 336, col. 2, para. 3, lines 1-3, para. 3, lines 1-4 and para. 4, lines 1-3). However, Robertson et al. teaches the identification of chimeric mice by the detection of proviral sequences, a transgene, into the genome of suspected chimeric mice (page 446, col. 2, para. 2). Thus, given the teachings of Watanabe et al. in view of Robertson et al., it would have been obvious to the ordinary artisan at the time of filing of the present application to make human animal chimeric embryos to determine the localization of donor cells in recipient embryos by the presence of integrated transgene sequences. Motivation is provided by Robertson et al. which states proviral marker sequences provide a set of markers for chromosome linkage analysis (page 447, col. 2, para. 1). A reasonable expectation of success is provided as the claims state only chimeric human-animal embryos, without stating any size or age limitation, or developmental potential. Thus for achieving such an embryo, which can be as small as one cell, Watanabe et al. in view of Robertson et al. provides sufficient teachings and motivation

No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is (703) 308-1126. The examiner can normally be reached on Monday to Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian R. Stanton, can be reached on (703) 308-2801. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP ~~1800~~ 1630

Dr. D. Crouch
March 17, 1999